EXTENDED REPORT

Incidence of lymphoma in a large primary care derived cohort of cases of inflammatory polyarthritis

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Ann Rheum Dis 2006;**65**:617–622. doi: 10.1136/ard.2005.044784

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Accepted 26 September 2005
Published Online First 25 October 2005

Objective: To determine the risk of lymphoma in a primary care derived cohort of new onset cases of inflammatory polyarthritis and assess the contribution of disease severity and standard immunosuppressive treatment.
Design: Prospective cohort study.
Methods: 2105 subjects with new onset inflammatory polyarthritis were recruited to the Norfolk Arthritis Register (NOAR) and followed annually for (median) 8.4 years. Occurrence of lymphoma was determined by annual morbidity review and linkage to the central hospital database serving the NOAR area. Cases of lymphoma were verified by record review. Standardised incidence ratios (SIRs) for lymphoma were calculated compared with the local, age, sex, and calendar year expected rates. Stratified analyses were undertaken for various markers of disease severity and treatment history.
Results: There were 11 cases of lymphoma during 15 548 person years of follow up, the majority of which were of large B cell type. Compared with the local population the SIR was 2.4 (95% confidence interval, 1.2 to 4.2). The risks in cases classified as rheumatoid arthritis, ever rheumatoid factor positive, or ever treated with DMARDs were all higher, the highest risk group being those treated with methotrexate: SIR = 4.9 (1.8 to 10.6).
Conclusions: There was a doubling in risk of lymphoma in new onset cases of inflammatory polyarthritis. Patients with the most severe disease were twice as likely as other patients to develop lymphoma. These results need to be taken into account when considering reported increased risks of lymphoma compared to background population risk in users of new biological agents.

There are consistent reports that rheumatoid arthritis is associated with the development of lymphoma. Reported risk ratios for the development of lymphoma, compared with the general population range from 1.9 up to 2.7.[1–6] By contrast, two studies did not find a significant increase in lymphoma risk.[7 8] There are very few data from true population inception cohorts, though in one large recent study from Sweden there was also a doubling of lymphoma risk in a cohort of 3000 incident cases.[2] It has been suggested that the increased occurrence of lymphoma is primarily driven either by the inflammatory process of the rheumatoid arthritis itself or by the use of immunosuppressive treatment.

Evidence supporting a relation with disease severity comes from several studies.[1 9–14] Specifically, various factors predict the occurrence of lymphoma, including a raised erythrocyte sedimentation rate (ESR), reduced haemoglobin, Steinbroker functional class, and the presence of extra-articular manifestations.[9 11 14] Conversely, there has been concern over the possibility of increased risk of lymphoma resulting from the use of certain treatments in patients with rheumatoid arthritis, including methotrexate[13] and azathioprine.[15 16] The association between methotrexate use and lymphoma is supported primarily by case report findings of remission of lymphomas upon withdrawal of methotrexate.[13 17–19] So far, no controlled studies have found evidence to suggest that those patients using methotrexate are at a greater risk of lymphoma than other rheumatoid patients.[20 21] Further, it is reasonable to suggest that the effective use of immunosuppressive drugs could actually counter lymphoma risk by reducing the severity of the disease.[22]

There are several case reports of lymphoma developing in patients treated with anti-tumour necrosis factor (TNF) agents.[23–25] Further, three studies have found the incidence of lymphoma in anti-TNFα treated patients to be higher than the general population rates.[2 6 26] However, such an increase may be explained by the underlying disease rather than the treatment. These agents are increasingly likely to be used earlier in the disease[27] and hence there is a need to understand the background incidence of lymphoma in such early cases of rheumatoid arthritis.

We have investigated whether there is an increased incidence of lymphoma in a large primary care based incident cohort of patients with inflammatory polyarthritis. We have also examined the role of disease severity factors and treatment with disease modifying anti-rheumatic drugs (DMARDs) on any such apparent risk.

METHODS

Summary of design

A prospective study was conducted following up a large primary care based incident cohort of patients with inflammatory polyarthritis. The number of lymphoma cases observed was compared with the number of expected lymphomas calculated using regional rates. Standardised incidence ratios compared with the general population and relative risks within the cohort after stratification for disease severity variables were calculated.

Subjects

The cohort used in this analysis was obtained from the Norfolk Arthritis Register (NOAR), based in Norwich, UK. The methods used for recruitment of patients into NOAR are described in detail elsewhere.[28] In brief, from 1990 patients

Abbreviations: DMARD, disease modifying antirheumatic drug; HAQ, health assessment questionnaire; NHL, non-Hodgkin's lymphoma; NOAR, Norfolk Arthritis Register; RF, rheumatoid factor; SIR, standardised incidence ratio

Table 1 Cohort characteristics

Age at onset of rheumatoid arthritis (years) (mean (SD))	55.6 (16.1)
Female sex (n (%))	1408 (67)
Delay from onset to start of follow up (months) (median)	12
Cumulative ACR criteria at fifth assessment positive (n (%))	1237 (59)
Ever RF positive (n (%))	681 (35)*
Used DMARD ever (n (%))	986 (47)
Used methotrexate ever (n (%))	582 (28)
Disease duration† at baseline (months)	
1st quartile	12
Median	12
3rd quartile	34.5
Maximum	60
Duration‡ of follow up (years) (mean (SD))	7.4 (2.3)

*Based on 1959 results.
†From inflammatory polyarthritis onset to baseline assessment.
‡From inflammatory polyarthritis onset to end of follow up.
ACR, American College of Rheumatology; DMARD, disease modifying antirheumatic drug; RF, rheumatoid factor.

aged 16 years or older who presented to their primary care physician with synovitis of two or more joints lasting for longer than four weeks were referred to NOAR. All subjects underwent a structured interview and physical examination at baseline, conducted by a trained research nurse, and serum was taken for rheumatoid factor. This analysis comprises all subjects recruited between 1 January 1990 and 31 December 1999.

Follow up

Patients were followed annually by a research nurse and details of all prescribed drugs were obtained, along with clinical data on disease activity and severity. Subjects whose arthritis was considered to be explained by another definite rheumatological disorder were subsequently excluded. The 1987 American College of Rheumatology (ACR) criteria for rheumatoid arthritis[29] were applied annually and subjects categorised as having rheumatoid arthritis if they ever satisfied the criteria, with the remaining subjects categorised as having undifferentiated inflammatory polyarthritis. Hand and foot radiographs were scored for the presence of erosions as described elsewhere.[30]

Lymphoma incidence was primarily established by linkage of the cohort with the electronic records system of the region's only major hospital. Such data were only available from 1995. Details of co-morbid conditions were also obtained, at interview, during each annual follow up. In addition, linkage to the National Death Register provided data on the date and cause of death where lymphoma was mentioned on the death certificate. Patient's notes and histological reports were reviewed to confirm the diagnosis of lymphoma, and the histological type of each case of lymphoma was recorded where available.

Analysis

Lymphoma cases were excluded from analysis if they occurred within 12 months of onset of the symptoms of inflammatory polyarthritis so as to reduce the likelihood that the arthritis postdated the onset of lymphoma. The incidence of lymphoma per 10 000 person-years was calculated for the entire cohort and then again for subgroups based on age and sex. As hospital linkage data were only available for the period starting 1 January 1995, analysis was restricted to the person-years of follow up after that date. Thus follow up time was calculated from the date of inflammatory polyarthritis onset or January 1995 (whichever was latest) until death, lymphoma diagnosis, emigration, or 31 March 2004 (the end of the study period). The incidence was then compared with expected rates calculated from 10 year age, sex, and calendar year specific rates obtained from the East Anglia Cancer Intelligence Unit (see acknowledgements) and standardised incidence rate (SIR) ratios with their 95% confidence intervals were calculated. A subanalysis of patients with recent onset inflammatory polyarthritis (those patients with symptoms lasting less than one year at baseline assessment) was also conducted. The influence of disease severity and activity on the risk of lymphoma was assessed by calculating SIRs after stratifying by age, sex, cumulative rheumatoid arthritis status (ACR criteria), rheumatoid factor status, erosive joint history, health assessment questionnaire (HAQ) score at fifth ''anniversary'' (the fifth assessment following the baseline interview), and exposure to DMARDs in general and methotrexate in particular. Finally, Poisson regression was used to model the relative risks of lymphoma for each of the above factors.

Results

Between 1990 and 1999, NOAR recruited 2749 patients. In all, 587 were subsequently diagnosed with a condition other than rheumatoid arthritis or psoriatic arthritis and were excluded from the analyses. Seven patients with onset of inflammatory polyarthritis before 1990 and one patient with

Table 2 Clinical and histological details of lymphoma cases

ID	Histological type	Node affected	Age at IP onset (y)	Sex	MTX use duration (y)	IP disease duration (y)	RA+	RF+
1	High grade diffuse large B cell lymphoma	Lymph node, right axilla	63	F	0	13.0	Yes	Yes
2	High grade diffuse large B cell lymphoma	Pelvis	58	F	7.2	12.1	Yes	No
3	Centroblastic B cell lymphoma	Bone marrow	64	M	0.8	6.1	Yes	Yes
4	Centroblastic B cell marginal zone lymphoma	Spleen, hilar lymph node	67	F	0	9.1	Yes	Yes
5	High grade centroblastic B cell lymphoma	Lymph node, right axilla	57	M	0.2	13.8	Yes	No
6	Diffuse large B cell lymphoma	Nasal duct	50	F	0	12.3	Yes	Yes
7	Diffuse large B cell lymphoma	Postnasal mucosa, left supraclavicular lymph node	65	M	0.2	8.4	Yes	Yes
8	Diffuse large B cell lymphoma	Lymph node, right axilla	79	F	0.2	3.5	No	*
9	Diffuse large B cell lymphoma	Left supraclavicular lymph node	65	F	0	6.1	No	No
10	Nodular sclerosing Hodgkin's disease	Retroperitoneal and mesenteric lymph nodes	51	M	0	12.3	Yes	No
11	Unknown non-Hodgkin's lymphoma	Unknown	61	M	7.0	9.5	Yes	Yes

*Missing data.
ID, identification number; IP, inflammatory polyarthritis; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; y, years.

Table 3 Incidence of lymphoma

Group	Total follow up (person-years)	Number of lymphomas	Incidence per 10 000 person-years	95% CI
Overall	15 548	11	7.07	3.53 to 12.66
Male	10 608	5	10.12	3.29 to 23.61
Female	4 940	6	5.66	2.08 to 12.31
Age ⩽49 y	3 425	0	0.00	0.00 to 10.77
Age 50–69 y	7 017	6	8.55	3.14 to 18.61
Age ⩾70 y	5 105	5	9.79	3.18 to 22.86
RA–	6 273	2	3.19	0.39 to 11.52
RA+	9 274	9	9.70	4.44 to 18.42

CI, confidence interval; RA, rheumatoid arthritis; y, years.

missing year of death were excluded. The electronic linkage allowed follow up of all but 49 of the remaining subjects who died before linkage with the hospital data. The disease characteristics of the remaining 2105 patients are shown in table 1.

The patients had a median follow up in this study of 8.4 years with a total follow up of 15 548 person-years. During this period 10 cases of non-Hodgkin's lymphoma (NHL) and one case of Hodgkin's disease were identified using the hospital record linkage. No additional cases were revealed using either the death certificates or the annual follow up interviews as described above. Indeed only three of these patients reported having ever had lymphoma in surveys undertaken during the follow up.

Compared with the overall population, patients diagnosed with lymphoma were slightly older (62 *v* 55 years) and more likely to be male (45% *v* 33%). They were also more likely to meet the ACR rheumatoid arthritis criteria applied cumulatively at the fifth assessment (82% *v* 59%). Rheumatoid factor positivity (60% *v* 35%), ever received DMARD (64% *v* 47%) including ever received methotrexate (55% *v* 27%), and radiological erosions (70% *v* 48%) were all more common in the lymphoma patients. Patients diagnosed with lymphoma were more likely to have an HAQ score greater than 1.0 at their fifth assessment (71% *v* 45%).

Histological records were obtained for 10 patients and the results can be seen in table 2. All cases of NHL were of the B cell type with six of these being diffuse large B cell lymphomas. Five of the 11 patients diagnosed with lymphoma died during a mean (SD) follow up of 9.6 (3.4) years. Lymphoma was the underlying cause of death in two of these cases, a contributory cause in one case, and was not mentioned at all on the death certificates of two cases.

The incidence rates per 10 000 person-years overall and by age and sex are shown in table 3. Incidence was higher in men than in women and was highest in those aged 70 years or older at onset of inflammatory polyarthritis, as well as in those who met the ACR criteria at their fifth assessment. The SIR of lymphoma (compared with the expected regional incidence) for this cohort of patients with inflammatory polyarthritis was 2.4 (95% confidence interval (CI), 1.2 to 4.2). When the analysis was restricted to cases with recent onset inflammatory polyarthritis (post-1994), the risk was slightly but not significantly lower: SIR = 2.0 (0.6 to 5.2).

The influence of various disease and treatment factors on lymphoma incidence was then calculated, first in comparison with the local population by computing strata specific SIRs, and then (where relevant) within the NOAR cohort by computing age and sex adjusted relative risks (table 4). Thus, compared with general population expectations, those patients who were classed as rheumatoid arthritis positive at the fifth assessment following baseline interview, had ever tested positive for rheumatoid factor (RF), had ever been treated with any DMARD, methotrexate, or corticosteroids, had an HAQ score greater than 1 at the fifth assessment, or had evidence of erosive joint disease were three to five times more likely to be diagnosed with lymphoma than the general population (table 4). By contrast, those who were either rheumatoid arthritis or RF negative throughout their follow up were at a small but statistically non-significantly increased risk. There seemed to be little difference between men and women, whereas those aged from 50 to 69 had a higher relative risk of lymphoma than those 70 years or older.

Within the cohort, the same disease severity factors were all associated with an approximate doubling in risk of lymphoma, though only with methotrexate use did the 95% confidence interval not span unity (RR = 3.3 (95% CI, 1.0 to 10.8)). There was substantial confounding between these factors and thus, for example, the increased risk from methotrexate use may be explained by disease severity or vice versa. Although the numbers were small we undertook a multivariate analysis to investigate the effect of methotrexate on lymphoma risk after adjusting for presence of erosions, RF, HAQ at fifth assessment, and five year cumulative rheumatoid arthritis status. Owing to a high correlation between methotrexate and these disease severity indicators, it was not possible to tease out any independent effects. As an example, adjusting methotrexate use for RF status attenuated the risk from the former to an RR of 2.2 (95% CI, 0.5 to 8.6). Tests for interaction between predictors were conducted, but no evidence for any specific interaction was found. Finally, while the SIRs for disease duration suggest a possible trend for decreasing risk with time (when compared with the general population), when considering the risk with duration within the cohort, the data suggest that there is no such association.

DISCUSSION

Patients in this primary care cohort of new onset cases with inflammatory polyarthritis had at least a twofold increased risk of the development of lymphoma when compared with the general population. The risk of lymphoma was further increased when we considered only those patients with markers of severe disease. The strongest risk factor was exposure to methotrexate; this may be explained, at least in part, by greater disease severity in that group, and there is some evidence that patients with rheumatoid arthritis who use methotrexate have somewhat more severe and active inflammatory disease overall (tables 5 and 6).

There are, however, some limitations that need to be discussed. Owing to the small number of events studied, the confidence intervals calculated for SIRs and relative risks were wide. This restricts the inferences that can be made about the magnitude of any effect of immunosuppressive drug exposure or disease severity. As such, it was not possible to investigate whether these two contributory factors interact, or the nature of any such interaction. The study was, however, able to assess incidence in over 15 000 person-years of exposure in this primary care derived cohort, and this

Table 4 Standardised incidence ratio by severity and treatment factors

	Observed (O)	Expected (E)*	SIR (O/E)	95% CI	RR (estimated)†	95% CI
Sex						
Female	6	2.77	2.17	0.80 to 4.72	1	–
Male	5	1.88	2.66	0.86 to 6.21	1.23	0.38 to 4.01
Age group						
Age ⩾70 y	5	2.24	2.24	0.73 to 5.22	1	–
Age 50 to 69 y	6	1.91	3.14	1.15 to 6.83	1.40	0.42 to 4.60
RA						
RA−	2	1.58	1.27	0.15 to 4.58	1	–
RA+	9	3.07	2.94	1.34 to 5.57	2.32	0.50 to 10.71
RF ever‡						
RF−	4	2.74	1.46	0.40 to 3.74	1	–
RF+	6	1.68	3.58	1.31 to 7.79	2.45	0.69 to 8.66
Treatment						
DMARD never	4	2.50	1.60	0.44 to 4.10	1	–
DMARD ever	7	2.14	3.27	1.31 to 6.73	2.04	0.60 to 6.96
MTX never	5	3.41	1.47	0.48 to 3.42	1	–
MTX ever	6	1.24	4.86	1.78 to 10.57	3.31	1.01 to 10.81
Steroids never	5	3.20	1.56	0.51 to 3.65	1	–
Steroids ever	6	1.44	4.16	1.53 to 9.05	2.65	0.81 to 8.66
HAQ at 5th assessment following registration§						
HAQ 5th <1	2	1.41	1.42	0.17 to 5.12	1	–
HAQ 5th >1	5	1.20	4.18	1.36 to 9.75	2.95	0.57 to 15.19
Erosion history¶						
Erosive−	3	1.62	1.85	0.38 to 5.40	1	–
Erosive+	7	1.89	3.70	1.49 to 7.63	2.00	0.52 to 7.75
Disease duration** (y)						
<5	1	0.14	7.08	0.18 to 39.5	Treating disease duration as a continuous variable	
5 to 10	5	1.96	2.54	0.83 to 5.93		
10 or more	5	2.54	1.97	0.64 to 4.60	0.95	0.74 to 1.21

*Number of lymphomas expected if incidence rate of general population applied.
†Age and sex adjusted.
‡Based on 1959 assessments.
§Based on 1154 assessments.
¶Based on 1441 assessments.
**At end of follow up, based on quartiles of follow up.
CI, confidence interval; DMARD, disease modifying antirheumatic drug; HAQ, health assessment questionnaire; MTX, methotrexate; RA, rheumatoid arthritis; RF, rheumatoid factor; RR, relative risk; y, years.

denominator was of sufficient size to allow the detection of several statistically significant overall increased risks.

As mentioned above, the option to link with the hospital admissions system only provided data on cases occurring after January 1995. The analysis therefore selectively excluded both from the numerator the cases, and from the denominator the follow up time, that occurred before this date. A subgroup analysis was thus undertaken restricting inclusion to only those subjects recruited with a symptom onset after 1 January 1994 (to allow for the one year lag phase), and the estimate of overall lymphoma risk was neither statistically increased compared with the general population nor statistically different from the results of the main analysis. Further, owing to the small numbers involved (four cases of lymphoma), analysis of the effect of predictors in this case was considered unreasonable. The one year lag period was also arbitrary. The true onset date for lymphoma cannot be obtained reliably and the only practical option is to date the onset as the date of diagnosis. It is clearly appropriate to allow for a lag period following the onset of inflammatory polyarthritis before allocating a lymphoma occurrence as post-arthritis, although in this study no cases of lymphoma were diagnosed during this period.

Ascertainment of the lymphoma cases in the inflammatory polyarthritis cohort were derived using a different data source from that obtained for the comparison cohort. One concern is that the more intensive follow up of the inflammatory polyarthritis cases will identify a higher

Table 5 Characteristics of patients with and without rheumatoid arthritis

	Did not meet RA criteria at 5th assessment	Met RA criteria at 5th assessment
HAQ* overall (mean (SD))	0.86 (0.72)	0.82 (0.71)
HAQ* overall (median)	0.70	0.63
Tender joint count (mean)	4.46	9.96
Swollen joint count (mean)	1.94	6.75

*Based on 2096 cases.
HAQ, health assessment questionnaire; RA, rheumatoid arthritis.

Table 6 Characteristics of patients with rheumatoid arthritis by history of methotrexate use

	Never used methotrexate	Ever used methotrexate
HAQ* overall (mean (SD))	0.79 (0.70)	0.86 (0.74)
HAQ* overall (median)	0.71	0.73
Tender joint count* (mean)	9.98	9.92
Swollen joint count* (mean)	6.46	7.21

*Based on 1237 cases.
HAQ, health assessment questionnaire.

Table 7 Risk of lymphoma in other rheumatoid arthritis cohorts compared with appropriate populations

Study	Cohort details	Site	SIR	95% CI
Finland, 1978[4]	RA	Lymphoma	2.7	1.9 to 3.7
UK, 1984[33]	RA	Haematopoietic	8.7	p<0.001
USA, 1985[8]	RA	Lymphoma	1.2	0.2 to 3.0
UK, 1988[16]	RA: not treated with AZA	Lymphoproliferative malignancies	4.8	0.58 to 17.2
Sweden, 1993[3]	RA	Lymphoma	1.98	1.5 to 2.6
Canada, 1997[7]	RA	NHL	0.55	0.11 to 1.6
Denmark, 1996[5]	RA	NHL	2.4	1.9 to 2.9
Sweden, 2003[1]	RA (hospital inpatients)	Lymphoma	2	1.83 to 2.17
USA, 2004[6]	RA: treated with anti-TNF, MTX, or none at all	Lymphoma	1.9	1.3 to 2.7
Sweden, 2005[2]	Incident RA	Lymphoma	2.0	1.0 to 3.5
Current study (Norfolk, UK)	IP	Lymphoma	2.34	1.18 to 4.24

AZA, azathioprine; CI, confidence interval; IP, inflammatory polyarthritis; MTX, methotrexate; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; SIR, standardised incidence ratio; TNF, tumour necrosis factor.

proportion of the lymphomas occurring, whereas the regional cancer registration data may underascertain the true number of cases. As a test of this, however, all the lymphoma cases ascertained from the NOAR cohort were in fact registered with the regional registry, so it is unlikely there was a serious differential ascertainment of cases between the inflammatory polyarthritis cohort and the background population.

The use of local hospital admission data to ascertain lymphoma cases is subject to the error that some cases of lymphoma were missed as a result of patients attending different hospitals. As the hospital from which these data were obtained is the only main hospital serving the study region, it is highly unlikely that this would have a substantial effect on our findings. Annual survey of the subjects by the study nurses and examination of death certificates did not identify any additional cases. Further, any such missed cases would imply that the true risk of lymphoma in these patients with inflammatory polyarthritis is actually greater than our data suggest.

One difference between this study and the previous work[1–6] is that it included all patients with inflammatory polyarthritis rather than being restricted to those who met rheumatoid arthritis classification criteria at baseline.[31 32] The use of such a cohort of patients with inflammatory polyarthritis, as opposed to rheumatoid arthritis, results in the inclusion of those with generally less severe disease. Interestingly, despite the primary care base for recruitment, when analyses were restricted to those patients who satisfied the ACR 1987 rheumatoid arthritis criteria, the risk of lymphoma was increased threefold in comparison with the general population.

This study has several strengths. This is the first study of lymphoma in a primary care derived cohort of patients with inflammatory polyarthritis, removing any possible bias resulting from the use of hospital or clinic based patients. Furthermore, as this cohort was truly prospective—unlike studies based on retrospective record review—the collection of data on disease severity and use of DMARDs was standardised. The electronic linkage also allowed virtually complete data with only 57 patients (2.7%) being excluded from follow up, as detailed previously.

The results of our study are consistent with the findings from studies in rheumatoid arthritis. The apparent predominance of diffuse large B cell lymphomas has been observed previously.[10 13 21] More importantly, as can be seen in table 7, the relative risk of lymphoma in our cohort was very similar to many other studies. This is of great interest, as patients in the NOAR cohort comprise a broader spectrum of rheumatoid arthritis severity than those from other rheumatoid populations. Thus it is not necessary to have severe disease to demonstrate an increased risk, although in NOAR, as in other cohorts,[8] severity was a marker for even greater risk.

Exposure to biological agents was rare in this cohort and only seven patients were given these (etanercept in all cases). None of these patients developed lymphoma.

In summary, this study confirmed that there is an excess risk of lymphoma in the decade following new onset of inflammatory polyarthritis compared with the general population. Much of this risk is restricted to those cases with high disease severity or the use of standard DMARDs including methotrexate, or both, although an increased risk in cases with milder disease is also suggested. These data stress the need for an appropriate control cohort for comparisons of the long term adverse effects of novel drugs for rheumatic diseases. Unfortunately, it remains uncertain whether the increased occurrence of lymphoma is attributable to rheumatoid arthritis specifically or to the inflammatory process of polyarthritis in general. The risks observed in this study were independent of any influence of biological therapy.

ACKNOWLEDGEMENTS

The Norfolk Arthritis Register (NOAR) is funded by the UK Arthritis Research Campaign. JF is supported by an educational grant from Bristol Myers Squibb Inc. The substantial support of Professor David Scott and clinical colleagues at the Norfolk and Norwich Hospital and the local primary care physicians is gratefully acknowledged. We are also grateful to Helen Coffey for undertaking the linkage to the hospital record systems and to the East Anglia Cancer Intelligence Unit for providing the comparison population data.

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